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Blood glucose, glucose balance and disease-specific survival after prostate cancer diagnosis in the Finnish Randomized Study of Screening for Prostate Cancer

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Tyypin 2 diabetes on aiemmissa tutkimuksissa yhdistetty huonoon eturauhassyövän ennusteeseen. Hyperglykemian vaikutus eturauhassyövän etenemiseen on kuitenkin epäselvä. Tutkimme hyperglykemian ja eturauhassyöpäkuolleisuuden yhteyttä. Kohorttina käytimme 1,770 miestä, joilla oli diagnosoitu eturauhassyöpä suomalaisen eturauhassyövän seulontatutkimuksen (FinRSPC) aikana vuosina 1995-2009. Näille osallistujille oli saatavissa myös tietoa paastoverensokerimittauksista Fimlabin tietokannasta. 1,398 osallistujalle oli saatavissa tietoa HbA1c-mittauksista. Tiedot diabeteslääkkeiden käytöstä saatiin Kansaneläkelaitoksen (Kela) reseptitietokannasta. Aikariippuvaista Coxin regressioanalyysiä hyödynnettiin riskisuhteiden ja 95% luottamusvälien estimointiin eturauhassyöpäkuoleman suhteen diabeettisilla, heikentyneen glukoosinsietokyvyn omaavilla (IGT) ja normoglykeemisillä miehillä.

Diagnoosin jälkeisen 9.9 vuoden mediaaniseuranta-ajan aikana 182 miestä kuoli eturauhassyöpään. Kasvaimen levinneisyysasteen, PSA-tason diagnoosin aikaan, ja Gleason pisteytyksen vakioimisen jälkeen diabeettiset paastosokeriarvot eturauhassyöpädiagnoosin jälkeen liittyivät korkeampaan eturauhassyöpäkuoleman riskiin verrattuna normoglykeemisiin miehiin. Kohonneen riskin yhteys oli suurin osallistujilla, joilla oli diagnoosivaiheessa paikallinen syöpä. Riskin kohoaminen oli havaittavissa jopa viisi vuotta edeltävästi otetuissa diabeettisissa verensokeritasoissa. Diabeettiset verensokeritasot ennen diagnoosia eivät olleet yhteydessä kohonneeseen eturauhassyöpäkuoleman riskiin.

Tutkimuskohorttimme viittaa siihen, että eturauhassyöpäpotilailla, joilla on diabeettinen paastoverensokeritaso, on korkeampi tautispesifinen kuolleisuus.

Avainsanat: glukoosi, glykatoitunut hemoglobiini, eturauhassyöpä, eloonjääminen

Tämän julkaisun alkuperäisyys on tarkastettu julkaisevan tahon puolesta osana normaalia artikkelin hyväksymisprosessia.

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Blood glucose, glucose balance and disease-specific survival after prostate cancer diagnosis in the Finnish Randomized Study of Screening for Prostate Cancer

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ABSTRACT

Introduction: Diabetes mellitus has been linked with adverse prostate cancer (PCa) outcomes. However, role of hyperglycemia in PCa progression is unclear. We evaluated the link between hyperglycemia and PCa survival among Finnish PCa patients.

Methods: The study cohort included 1,770 men with data on fasting glucose and diagnosed with PCa within the Finnish Randomized Study of Screening for PCa in 1995-2009. Additionally, 1,398 men had data on glycated haemoglobin (HbA1c). Information on fasting glucose and HbA1c measurements was obtained from the regional laboratory database. Antidiabetic medication use was obtained from the prescription database of the Social Insurance Institution (SII). Time-dependent Cox regression analysis was used to estimate hazard ratios (HRs) and 95% confidence intervals for PCa death among diabetic, glucose intolerant (IGT), and normoglycemic men.

Results: During median follow-up of 9.9 years after the diagnosis, 182 men died from PCa. After adjustment for tumor stage, Gleason grade and PSA level at diagnosis, diabetic fasting glucose level after PCa diagnosis was associated with elevated risk of PCa death compared to normoglycemic men (HR 1.67 95% CI 1.18-2.36). The risk association was strongest among participants with localized cancer at diagnosis; HR 2.39, 95% CI 1.45-3.93. The risk elevation was observed for glucose measurements taken up to five years earlier. Diabetic glucose levels measured before the diagnosis were not associated with PCa death.

Conclusion: Our study cohort suggests an increased risk of PCa death in men with diabetic fasting blood glucose levels, supporting the role of hyperglycemia as risk factor for PCa progression.

Running head: blood glucose and prostate cancer

Keywords: Glucose, Glycated haemoglobin, Prostate Cancer, Survival

INTRODUCTION

Type II diabetes has been linked with increased risk of many cancer types, possibly through hyperglycaemia and hyperinsulinemia [1]. For prostate cancer (PCa), the findings are more controversial. Several studies have found a decreased risk of PCa in men with type II diabetes mellitus [2]. These results are supported by androgen receptor downregulation by high glucose level in androgen-sensitive PCa cells [3]. This in theory could mitigate testosterone stimulation of cancer cells. However, in other studies hyperinsulinemia, a key feature besides hyperglycaemia in type II diabetes, is associated with an increased risk of PCa [4][5], possibly due to increased IGF-1 activity in the prostatic tissue [6].

Metabolic syndrome and obesity likely increase PCa progression and mortality [7]. Obesity has also been linked to more aggressive PCa subtypes [8]. However, knowledge on the role of individual components of metabolic syndrome is insufficient. Especially data on hyperglycaemia, a key component of type II diabetes and metabolic syndrome, and its correlation to PCa progression and mortality is scarce and contradictory.

We investigated the association between hyperglycaemia and risk of disease-specific death among men with PCa in the Finnish Randomized Study of Screening for PCa. In addition to fasting glucose, we analysed glycosylated haemoglobin (HbA1c), which gives an approximate of patient's average blood glucose over 120 days. To assess the effects of anti-diabetic medication on the risk association we analysed separately the risk of PCa death both before and after anti-diabetic medication in PCa patients prescribed with blood glucose lowering drugs.

MATERIALS AND METHODS

Study cohort

The Finnish Randomized Study of Screening for PCa (FinRSPC) is the largest component of the European Randomized Study of Screening for PCa (ERSPC) [9]. Between 1996-1999, 80,458 Finnish men aged 55-69 years at baseline were randomized either to be screened for PCa with prostate-specific antigen (PSA) measurements at four-year intervals, or to be followed through national registries. Prevalent PCa cases were excluded at baseline. The intervention, completed in 2008, consisted of three screening rounds. Follow-up for PCa incidence and mortality still continues.

The present study cohort consists of 6,537 men diagnosed with PCa within the FinRSPC study population between 1996 and 2009. For each case, information on the date of diagnosis, age, tumor stage, Gleason score and treatment as well as date of death (available until end of 2015) were obtained from medical files and the nationwide Finnish Cancer Registry. Causes of death were obtained from Statistics Finland. Accuracy of information on PCa deaths was validated by the FinRSPC cause of death committee [9].

Information on medication use during 1995-2015 was extracted from the prescription database of the Social Insurance Institution (SII), which is a governmental institution to manage social security in Finland. SII provides reimbursements for purchases of physician-prescribed drugs. The benefits are available to all Finnish citizens. All reimbursed purchases are recorded at individual level in the SII database, which covers all of Finland. Cases were linked to their corresponding medical information by personal identification number. The information included records of use of antidiabetic medication, antihypertensive drugs, cholesterol-lowering statins, NSAIDs (nonsteroidal anti-inflammatory drugs), and aspirin, identified based on ATC codes.

Information on blood glucose level

Information on measurements of fasting blood and plasma glucose were extracted from the records of Fimlab, the largest medical laboratory service provider in the Pirkanmaa area. The records cover the results from all laboratory tests by Fimlab laboratories in the Pirkanmaa region. The records date back to 1978. Information included fasting blood glucose concentration in the plasma or blood and the serum glycosylated haemoglobin concentration (HbA1c). For each measurement, the date and the result were available. Fimlab data was linked to the study cohort using unique personal identification number. Out of 6,537 men, 1,770 had at least one fasting

blood/plasma glucose measurement. Of these 1,048 had at least one measurement before PCa diagnosis, 1,676 had measurements after. In total 1,398 had at least one HbA1c measurement, 323 before and 1,359 after the diagnosis. Consequently, these men were used in the statistical analysis. The individual blood glucose and HbA1c measurements were used to calculate the mean for every calendar year. Based on yearly mean fasting glucose level men were categorized to be normoglycemic (6.0 mmol/l or below), impaired glucose tolerance (6.1 to 6.9mmol/l), or diabetic (7.0mmol/l or over). Corresponding cut points for HbA1c were 38mmol/l or below for normoglycemic, 39-47mmol/l for impaired glucose tolerance, and 48mmol/l or higher for diabetes. The fasting glucose and HbA1c levels were determined separately for each calendar year between 1978-2016.

Statistical analysis

All cases with blood glucose measurements were included in the analysis, regardless of the absolute number of measurements.

Cox regression method was used to estimate hazard ratios (HRs) and 95% confidence intervals (95% CI) for PCa death by fasting glucose and HbA1c level. The time metric was years and months since PCa diagnosis. Cox regression model was adjusted for age as a continuous variable (age-adjusted analysis) and additionally for FinRSPC trial arm, Gleason score and tumor stage at diagnosis, use of other drugs (antihypertensive and cholesterol-lowering drugs, NSAIDs and aspirin) and PSA at diagnosis (multivariable adjusted analysis)

The impact of blood glucose on risk of PCa death was estimated separately for glucose levels before and after the diagnosis. The same was done for HbA1c. Glucose and HbA1c levels before PCa diagnosis were analysed as time-independent variables, taking into account results from all measurements performed between 1978 and the year of diagnosis. Glucose and HbA1c levels after PCa diagnosis were analysed as time-dependent variable, prospectively updating the level for each follow-up year after PCa diagnosis based on available measurements. Men with missing values on a given year were categorized into a separate category.

To evaluate possible effect modification by background variables subgroup analyses were performed stratified by tumor clinical characteristics (Gleason score, tumor stage and serum PSA at diagnosis), age at diagnosis stratified by median, primary treatment, and medication use. Finally, information on antidiabetic drugs use was used to estimate risk of PCa death separately by whether blood glucose decreased, increased or stayed the same after initiation of antidiabetic drugs.

Lag-time analysis was used to assess the long-term risk of death in PCa patients with elevated blood glucose levels. Blood glucose levels from a certain year were lagged forward in the follow-up time, e.g. in 5-year lag time analysis measurements from the first follow-up year were analysed on the sixth follow-up year. We estimated the risk of PCa death in relation to blood glucose measurements taken 1-20 years earlier. This allowed us to estimate how diabetic blood glucose measurements in the past predicted the prognosis of PCa patients. Both IGT and diabetic blood glucose levels were examined, with normoglycemic men as the reference group.

Statistical analyses were performed using “IBM SPSS Statistics 23” software.

RESULTS

Population characteristics

At least one fasting blood glucose measurement was available for 1,770 PCa (27.1%) cases, of whom 675 died (182 from PCa) during the median follow-up of 9.9 years after the diagnosis (Table 1). The median follow-up time was slightly shorter in diabetic patients (9.3 versus 10.1).

The proportion of Gleason 7 and 8-10 tumors was higher among men with diabetes or IGT compared to normoglycemic men. Also, the proportion of men with metastatic PCa at diagnosis was non-significantly higher in diabetic men (7.9% vs 4.8%, p = 0.064). Similarly, median PSA at diagnosis was higher in diabetic men (9.0 vs 7.4 ng/ml, p = 0.003) (Table 1).

Primary PCa treatment did not significantly differ by blood glucose level. Diabetic men were slightly less often managed surgically and received more often endocrine treatment compared to normoglycemic men.

Men with elevated blood glucose levels were more often users of antidiabetic drugs (73.0% in diabetic versus 3.5% in normoglycemic men, p <0.001) and antihypertensive drugs (91.7% versus 81.7%, respectively, p < 0.001)

Table 1. Population characteristics.

	Fasting blood glucose		
	Normoglycemic	IGT	Diabetic
n of cases	971	484	315
n of deaths	324 (33.4%)	181 (37.4%)	170 (54.0%)
n of prostate cancer deaths	76 (7.8%)	57 (11.8%)	49 (15.6%)
median follow up (IQR)	10.1 (7.0-12.9)	9.8 (6.8-12.5)	9.3 (5.0-13.3)
Gleason score; n (%)*			
6 or less	587 (60.4%)	245 (50.6%)	158 (50.2%)
7	244 (25.1%)	147 (30.4%)	82 (26.0%)
8-10	111 (11.4%)	77 (15.9%)	60 (19.0%)
Tumour stage; n (%)			
localized	894 (92.1%)	436 (90.1%)	286 (90.8%)
metastatic	47 (4.8%)	36 (7.4%)	25 (7.9%)
Median psa at diagnosis (IQR)	7.40	7.9	9.0**
Primary treatment; n (%)			
surgery	330 (34.0%)	154 (31.8%)	85 (27.0%)
radiation therapy	337 (34.7%)	170 (35.1%)	116 (36.8%)
endocrine therapy	180 (18.5%)	99 (20.4%)	79 (25.1%)

active surveillance/watchful waiting	116 (11.9%)	55 (11.4%)	31 (9.84%)
Medication use; n (%)			
statins	487 (50.2%)	262 (54.1%)	199 (63.2%)
antihypertensive drugs*	793 (81.7%)	406 (83.9%)	289 (91.7%)
antidiabetic drugs*	34 (3.50%)	86 (17.8%)	230 (73.0%)
nsaid	896 (92.3%)	457 (94.4%)	286 (90.8%)
aspirin	174 (17.9%)	78 (16.1%)	63 (20.0%)
Charlson comorbidity index; median (IQR)	2 (2-4)	2 (2-4)	3 (2-5)**

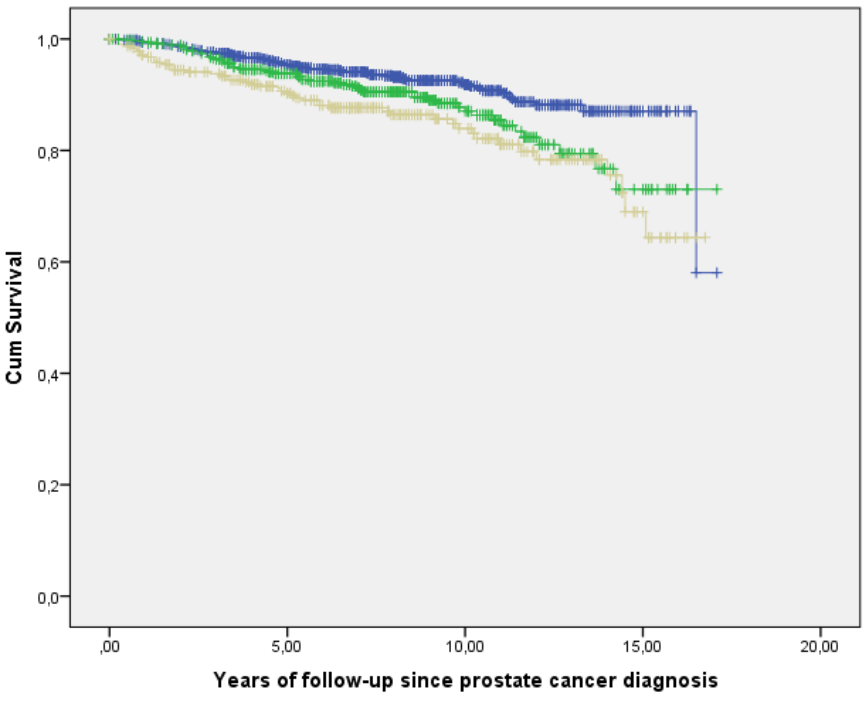
* P < 0.05 for difference by blood glucose level. Calculated with Chi-square test.

** p <= 0.003 for difference compared to normoglycemic men. Calculated with Mann-Whitney U-test

Risk of PCa death by fasting blood glucose level before and after diagnosis

The 5-year disease-specific survival proportions were 91.1%, 94.2% and 95.8% among diabetic, pre-diabetic and normoglycemic men, respectively (Supplementary figure 1). Compared to normoglycemic men, diabetic blood glucose levels after PCa diagnosis were associated with an increased risk of PCa death (multivariable-adjusted HR 1.67 95% CI 1.18-2.36) (Table 2). Similar risk increase was observed for IGT and diabetic blood glucose levels before PCa diagnosis only in the age-adjusted analysis.

Supplementary figure 1. Kaplan-Meier curves for prostate cancer-specific survival stratified by fasting blood glucose level. Study cohort of 6,537 men with prostate cancer from the Finnish Randomized Study of Prostate Cancer Screening.



The increased risk of PCa death by diabetic blood glucose level post-diagnosis

was observed in men with Gleason 6 or lower and Gleason 7 disease at diagnosis, not among men with Gleason 8-10 tumors (Table 2). The risk association between blood glucose level and risk of PCa death did not differ by PSA level.

When stratified by tumor stage, the risk increase by post-diagnostic blood glucose level was observed only among men diagnosed with non-metastatic cancer; both IGT and diabetic glucose levels were associated with increased risk of PCa death: HR 1.83 (0.89-3.76) for IGT, and HR 2.39 (1.45-3.93) for diabetic participants in this subgroup. Again, such findings were not observed for glucose levels before PCa diagnosis (Table 2).

Table 2. Risk of prostate cancer death by blood glucose level (normoglycemic level as the reference point). Cohort population of 1,770 men with prostate cancer diagnosed within Finnish Randomized Trial of Screening for Prostate Cancer.

	Risk of prostate cancer death							
	Blood glucose before diagnosis				Blood glucose after diagnosis			
	HR (95%CI)$_{age\text{-}adjusted}$		HR (95%CI)$_{multivariable\text{-}adjusted*}$		HR (95%CI)$_{age\text{-}adjusted}$		HR (95%CI)$_{multivariable\text{-}adjusted*}$	
	IGT	Diabetic	IGT	Diabetic	IGT	Diabetic	IGT	Diabetic
All prostate cancer cases	1.60 (1.02-2.53)	2.34 (1.47-3.73)	1.04 (0.65-1.68)	1.69 (1.05-2.72)	1.69 (0.99-2.89)	1.72 (1.22-2.42)	1.50 (0.87-2.56)	1.67 (1.18-2.36)
Gleason 6 or below	1.49 (0.47-4.70)	1.49 (0.38-5.81)	0.95 (0.28-3.17)	1.24 (0.30-5.12)	1.48 (0.37-5.28)	2.41 (1.07-5.45)	1.45 (0.36-5.80)	2.37 (1.05-5.37)
Gleason 7	1.61 (0.64-4.10)	3.63 (1.53-8.63)	1.76 (0.61-5.08)	3.69 (1.39-9.77)	0.79 (0.16-3.81)	2.68 (1.26-5.70)	0.67 (0.14-3.17)	2.26 (1.12-4.59)
Gleason 8-10	1.28 (0.70-2.36)	1.21 (0.62-2.36)	0.94 (0.50-1.78)	1.27 (0.64-2.52)	1.17 (0.58-2.37)	1.02 (0.64-1.63)	1.14 (0.56-2.34)	1.01 (0.63-1.63)
Localized cancer	1.82 (1.03-3.23)	2.12 (1.03-3.23)	1.65 (0.91-2.96)	1.52 (0.82-2.83)	2.36 (1.15-4.84)	2.46 (1.49-4.05)	1.83 (0.89-3.76)	2.39 (1.45-3.93)
Metastatic cancer	0.49 (0.23-1.04)	1.60 (0.77-3.35)	0.66 (0.29-1.52)	1.78 (0.77-4.08)	1.07 (0.46-2.48)	0.98 (0.60-1.61)	1.05 (0.45-2.45)	0.97 (0.59-1.59)
Serum PSA at diagnosis 7.31 or below	2.51 (0.97-6.52)	3.31 (1.27-8.63)	1.83 (0.64-5.20)	1.71 (0.62-4.77)	1.74 (0.62-4.89)	1.92 (0.98-3.76)	1.20 (0.43-3.39)	1.99 (1.01-3.91)
Serum PSA at diagnosis 7.32 or higher	1.10 (0.64-1.90)	1.98 (1.15-3.41)	0.69 (0.40-1.22)	1.66 (0.96-2.89)	1.37 (0.70-2.67)	1.38 (0.92-2.07)	1.40 (0.71-2.74)	1.45 (0.97-2.17)

IGT = Impaired glucose tolerance

* Calculated with Cox regression model with adjustment for age at PCa diagnosis, tumor Gleason grade and stage, PSA at diagnosis and FinRSPC study arm.

In analyses of HbA1c levels (Table 3), some suggestions of increased risk were noted for diabetic levels both before and after PCa diagnosis. However, the analyses were limited by low statistical power.

Table 3. Risk of prostate cancer death by glycated haemoglobin level (normoglycemic level as the reference point). Cohort population of 1,770 men with prostate cancer diagnosed within Finnish Randomized Trial of Screening for Prostate Cancer.

	Risk of prostate cancer death							
	HbA1c-level before diagnosis				HbA1c-level after diagnosis			
	HR (95%CI)$_{age\text{-}adjusted}$		HR (95%CI)$_{multivariable\text{-}adjusted*}$		HR (95%CI)$_{age\text{-}adjusted}$		HR (95%CI)$_{multivariable\text{-}adjusted*}$	
	IGT	Diabetic	IGT	Diabetic	IGT	Diabetic	IGT	Diabetic
All prostate cancer cases	1.30 (0.51-3.32)	2.14 (0.89-5.14)	1.21 (0.46-3.41)	1.33 (0.52-3.41)	2.02 (0.87-4.69)	1.79 (0.85-3.76)	1.81 (0.78-4.22)	1.86 (0.88-3.92)
Gleason 6 or below	-	-	-	-	4.50 (0.54-37.4)	3.68 (0.52-26.3)	4.35 (0.52-36.2)	3.80 (0.53-27.2)
Gleason 7	1.35 (0.22-8.43)	0.92 (0.13-6.61)	3.09 (0.32-29.7)	4.24 (0.23-80.0)	3.11 (0.35-27.9)	4.51 (0.63-32.3)	3.01 (0.33-27.1)	4.75 (0.66-34.0)
Gleason 8-10	1.37 (0.46-4.12)	2.43 (0.84-7.02)	1.62 (0.50-5.23)	2.03 (0.66-6.25)	0.87 (0.30-2.52)	0.97 (0.40-2.35)	0.71 (0.25-2.07)	0.76 (0.31-1.85)
Localized cancer	0.88 (0.27-2.90)	1.24 (0.40-3.84)	1.00 (0.31-3.20)	1.00 (0.30-3.31)	1.59 (0.61-4.09)	1.50 (0.67-3.35)	1.40 (0.54-3.61)	1.64 (0.73-3.68)
Metastatic cancer	4.89 (0.57-41.6)	8.86 (1.11-71.1)	5.03 (0.58-43.5)	9.04 (1.05-78.0)	2.48 (0.31-19.8)	2.58 (0.31-19.8)	2.35 (0.29-18.8)	2.21 (0.31-15.9)
Serum PSA at diagnosis 7.31 or below	1.06 (0.19-5.85)	2.04 (0.41-10.2)	1.00 (0.22-4.65)	1.00 (0.20-4.93)	1.82 (0.37-9.04)	1.80 (0.45-7.26)	1.08 (0.22-5.38)	1.72 (0.43-6.98)
Serum PSA at diagnosis 7.32 or higher	2.06 (0.67-6.35)	2.62 (0.92-7.51)	3.03 (0.86-10.6)	2.90 (0.86-9.82)	1.94 (0.71-5.29)	1.64 (0.68-4.00)	1.95 (0.71-5.35)	1.78 (0.74-4.31)

* Calculated with Cox regression model with adjustment for age at PCa diagnosis, tumor Gleason grade and stage, PSA at diagnosis and FinRSPC study arm.

Subgroup analysis

In subgroup analyses no significant effect modification was observed by age at diagnosis or primary treatment modality (Table 4).

Similarly, use of antihypertensive drugs, NSAIDs, or aspirin did not clearly modify the risk association between blood glucose and PCa death (Table 4). However, use of antidiabetic medication modified the risk association with diabetic glucose level, risk increase being observed only among men who did not use antidiabetic drugs, p for interaction = 0.022 in the diabetic group. Furthermore, participants with diabetic blood glucose levels after the diagnosis who were simultaneously taking statins had an increased risk of PCa death, but among men who were not statin users the risk increase was not significant; p for interaction = 0.019.

Table 4. Risk of prostate cancer death by blood glucose levels in subgroups stratified by age, primary treatment and medication use (normoglycemic level as the reference point). Cohort population of 1,770 men with prostate cancer diagnosed within Finnish Randomized Trial of Screening for Prostate Cancer.

	Risk of death overall			
	Blood glucose before diagnosis		Blood glucose after diagnosis	
	HR (95%CI)$_{multivariable\text{-}adjusted*}$		HR (95%CI)$_{multivariable\text{-}adjusted*}$	
	IGT	Diabetic	IGT	Diabetic
Age at diagnosis				
66 or younger	0.74 (0.25-2.19)	1.22 (0.45-3.27)	1.93 (0.84-4.43)	1.54 (0.88-2.71)
67 or older	1.22 (0.70-2.12)	1.84 (1.04-3.25)	1.26 (0.62-2.56)	1.73 (1.12-2.69)
Primary treatment				
Surgery	0.54 (0.06-5.28)	1.15 (0.11-11.9)	9.42 (0.98-91.0)	8.02 (1.11-58.0)
Radiation therapy	2.91 (1.08-7.81)	1.09 (0.31-3.87)	1.51 (0.49-4.62)	2.00 (0.99-4.06)
Endocrine therapy	0.82 (0.45-1.47)	1.76 (1.01-3.07)	1.01 (0.51-2.03)	1.27 (0.84-1.92)
Watchful waiting	-	-	-	-
Medication use				
Antidiabetic drugs				
Any	1.67 (0.47-5.93)	2.23 (0.67-7.49)	0.59 (0.22-1.64)	0.64 (0.26-1.57)**
None	0.96 (0.56-1.63)	1.81 (0.95-3.46)	1.48 (0.62-3.58)	1.88 (1.29-2.73)**
Statins				
Any	1.34 (0.56-3.19)	2.38 (1.03-5.48)	1.10 (0.40-3.03)	2.34 (1.24-4.40)***
None	1.01 (0.56-1.84)	1.70 (0.91-3.18)	2.15 (1.14-4.06)	1.29 (0.85-1.95)***
Antihypertensive drugs				

Any	1.20 (0.70-2.08)	1.95 (1.12-3.38)	1.36 (0.75-2.47)	1.60 (1.09-2.37)
None	0.94 (0.27-3.27)	0.87 (0.29-2.61)	2.80 (0.81-9.63)	1.98 (0.93-4.25)
NSAIDs				
Any	1.25 (0.76-2.05)	1.63 (0.96-2.76)	1.32 (0.75-2.33)	1.48 (1.04-2.12)
None	0.03 (0.00-2.53)	2.75 (0.66-11.5)	4.49 (0.74-27.2)	4.32 (1.05-17.8)
Aspirin				
Any	0.50 (0.14-1.77)	0.97 (0.16-5.75)	1.36 (0.25-7.60)	1.90 (0.69-5.26)
None	1.15 (0.69-1.92)	1.78 (1.07-2.96)	1.56 (0.89-2.75)	1.63 (1.11-2.36)

* Calculated with Cox regression model with adjustment for age at PCa diagnosis, tumor Gleason grade and stage, PSA at diagnosis and FinRSPC study arm.

** P for interaction = 0.022 in the group with diabetic fasting blood glucose level

*** P for interaction by statin use = 0.019

Impact of change in fasting blood glucose level after initiation of antidiabetic drug use

Change in blood glucose level after initiation of antidiabetic drug use did not clearly modify the risk association (Supplementary table 1); diabetic blood glucose level was associated with increased risk for PCa death. However, confidence intervals were wide and statistical significance was not reached.

Supplementary table 1. Risk of prostate cancer death by blood glucose level in relation to effectiveness of anti-diabetic medication (no change in blood glucose level as the reference point). Cohort population of 1,770 men with prostate cancer diagnosed within Finnish Randomized Trial of Screening for Prostate Cancer.

	Risk of prostate cancer death			
	Blood glucose level shift after anti-diabetic medication			
	$HR\ (95\%CI)_{age\text{-}adjusted}$		$HR\ (95\%CI)_{multivariable\text{-}adjusted*}$	
	Level fell	Level rose	Level fell	Level rose
All diabetic drugs combined	3.57 (1.44-8.87)	1.91 (0.69-5.26)	5.71 (2.12-15.4)	2.02 (0.68-5.96)
Insulin	3.28 (0.73-14.8)	4.77 (0.85-26.7)	4.14 (0.67-25.6)	7.75 (0.84-71.3)
Sulfonylurea Compounds	1.95 (0.66-5.77)	1.97 (0.52-7.46)	1.00 (0.30-3.31)	1.00 (0.21-4.72)
Glitazone	-	-	-	-
Metformin	2.07 (0.75-5.69)	1.24 (0.40-3.86)	3.21 (0.97-10.7)	1.27 (0.37-4.33)

* Calculated with Cox regression model with adjustment for age at PCa diagnosis, tumor Gleason grade and stage, PSA at diagnosis and FinRSPC study arm.

Lag-time analyses

Risk estimates remained increased similarly increased in 1-year and 5-year lag-time analyses (Table 5). In 10-year and 20-year lag-time analyses no increased risks were observed, but the confidence intervals were wide.

Table 5. Long-term association between fasting blood glucose level and prostate cancer death in lag-time analysis (multivariable adjusted*).

		Lag time			
	Main analysis	1yr	5yrs	10yrs	20yrs
Fasting blood gluose level	HR (95% CI)	HR (95% CI)	HR (95% CI)	HR (95% CI)	HR (95% CI)
Normal	Ref	Ref	Ref	Ref	Ref
IGT	1.50 (0.87-2.56)	2.07 (1.21-3.54)	2.03 (1.14-3.62)	1.03 (0.43-2.48)	0.97 (0.09-10.7)
Diabetic	1.67 (1.18-2.36)	1.90 (1.31-2.75)	1.51 (1.02-2.24)	1.22 (0.70-2.12)	1.33 (0.33-5.35)

* Calculated with Cox regression model with adjustment for age at PCa diagnosis, tumor Gleason grade and stage, PSA at diagnosis and FinRSPC study arm.

Risk of starting endocrine therapy

Post diagnostic diabetic blood glucose measurements were associated with an increased risk of starting endocrine therapy (multivariable adjusted HR 1.38, 95% CI 1.18-1.62). Nonetheless, direction of change in blood glucose level after initiation of endocrine therapy had no association with prostate cancer survival (Supplementary tables 2 and 3).

Supplementary table 2. Risk of initiation of endocrine therapy as the primary treatment by blood glucose level (normoglycemic level as the reference point). Cohort population of 1,770 men with prostate cancer diagnosed within Finnish Randomized Trial of Screening for Prostate Cancer.

	Risk of initiation of endocrine therapy			
	$HR\ (95\%CI)_{age\text{-}adjusted}$		$HR\ (95\%CI)_{multivariable\text{-}adjusted*}$	
	IGT	Diabetic	IGT	Diabetic
All prostate cancer cases	1.02 (0.79-1.34)	1.41 (1.20-1.65)	1.04 (0.80-1.36)	1.38 (1.18-1.62)

*Calculated with Cox regression model with adjustment for age at PCa diagnosis, tumor Gleason grade and stage, PSA at diagnosis and FinRSPC study arm.

Supplementary table 3. Risk of prostate cancer death by reaction of blood glucose level after initiation of endocrine therapy (no change in blood glucose level as the reference point). Cohort population of 1,770 men with prostate cancer diagnosed within Finnish Randomized Trial of Screening for Prostate Cancer.

	Risk of prostate cancer death			
	Blood glucose level shift after initiation of endocrine therapy			
	$HR\ (95\%CI)_{age\text{-}adjusted}$		$HR\ (95\%CI)_{multivariable\text{-}adjusted*}$	
	Level fell	Level rose	Level fell	Level rose
All endocrine therapy cases	0.97 (0.60-1.59)	0.64 (0.38-1.10)	0.84 (0.50-1.40)	0.59 (0.34-1.02)

*Calculated with Cox regression model with adjustment for age at PCa diagnosis, tumor Gleason grade and stage, PSA at diagnosis and FinRSPC study arm.

DISCUSSION

Diabetic fasting blood glucose levels after PCa diagnosis are associated with an increased risk of PCa death. IGT was generally not associated with risk increase. When stratified by tumor characteristics, the risk was modified by tumor stage, the association being stronger among men with localized PCa. Blood glucose level before PCa diagnosis had no association with PCa mortality.

Previous studies on this topic are scarce. Most earlier studies have evaluated self-reported diabetes or relied on antidiabetic medication use. In our study the definition of diabetes was made by measured blood glucose levels, therefore we were more likely to catch also untreated diabetes. Indeed, the risk increase by diabetic glucose level was strongest in men who were not antidiabetic drug users. Thus, antidiabetic treatment likely affects the cancer risks associated with diabetes, suggesting that the optimal way to study diabetes as cancer risk factor includes also non-treated diabetics. We were able to evaluate long-term associations between glucose level and PCa survival, and level after PCa diagnosis. This allowed more comprehensive analysis of diabetes as condition compared to previous studies

A meta-analysis containing 17 cohort studies found an increased risk of PCa death among patients with pre-existing diabetes mellitus (RR=1.29) [(10)]. Similar results were presented by another meta-analysis consisting of 11 cohort studies (RR=1.26) [(11)]. Furthermore, a cohort consisting of 11,920 participants found comparable risk association with diabetes mellitus and PCa progression (RR=1.23) [(12)]. Our study supports these findings.

Similar to our study, a weak correlation between hyperglycaemia and PCa death has been previously reported in men with intolerance for oral glucose load [(13)]. The study cohort in the earlier study was similarly sized as ours, but the mean follow-up time after PCa diagnosis was longer (27 vs 9.9 years). However, the blood glucose level groups were stratified by study population-specific

quartiles, whereas we used clinical cut-points for IGT and diabetes, producing greater generalizability.

Previously, increased overall cancer mortality has been reported in diabetic patients [11]. One possible explanation could be more aggressive tumor types among diabetics. A previous cohort study reported an increased risk of high-grade and metastatic PCa in hyperglycaemic participants [14]. Another cohort study found an association between high HbA1c-levels and higher Gleason scores in diabetic PCa patients [15]. However, a previous case-control study showed no association between diabetes and PCa aggressiveness [16]. Similarly, we have previously observed no association between antidiabetic drug use and Gleason score in the FinRSPC study population [17]. Diabetes has also been associated with lower serum PSA levels, which may affect the risk association; in a cohort of Finnish operatively managed PCa patients, diabetic men had more high-grade disease despite similar PSA levels compared to non-diabetic [18]. However, CaPSURE-study reported no association between diabetes mellitus and aggressive PCa in patients managed with radical prostatectomy [19].

Increased availability of glucose in the bloodstream supports and fuels rapid cancer cell proliferation [11]. High blood glucose levels have been proposed to activate genes regulating cell proliferation and migration *in vitro*, increasing their expression in cancer cells [20]. High blood glucose has also been linked to decreased apoptosis [11]. We have previously reported a link between SNPs in the genes of the glucose metabolic pathway and PCa risk and prognosis, further supporting importance of glucose metabolism for PCa progression [21]. Thus, PCa may be more aggressive and exhibit higher proliferative activity in diabetics compared to normoglycemic men, leading to worse survival as observed in our study. Nevertheless, we did observe the survival difference after adjustment for tumor grade, thus hyperglycemia is likely also an independent risk factor for PCa progression.

In type II diabetes mellitus, hyperinsulinemia accompanies persistently elevated blood glucose levels due to insulin resistance. Hyperinsulinemia contributes to tumor growth due to mitogenic effects on cells. Insulin sensitizes cells to other growth factors, such as insulin-like growth factors (IGFs), platelet-derived growth factor (PDGF), and vascular endothelial growth factor (VEGF). Thus, insulin increases cancer cell proliferation leading to faster tumor growth [22]. Insulin stimulates the production of IGF-1 in the liver, which further stimulates cell proliferation and inhibits apoptosis. Cancerous cells have a high expression of the IGF-1 receptor gene and high circulating IGF-1 levels associate with poorer prognosis in cancer patients [23]. Insulin also inhibits the production of insulin-like growth factor binding proteins (IGFBP – I and II), which bind and inhibit IGF-1. Without IGFBP, circulating active IGF-1 is more abundant, which results in increased tumor growth [23].

Our study cohort was fairly large and contained extensive information on participant and tumor characteristics. Particularly information of usage of anti-diabetic medication within the study cohort allowed us to analyse the effect of anti-diabetic drugs and its relation to risk of PCa death. In addition to fasting blood glucose levels, we also analysed the relation of HbA1c-levels and PCa death, eliminating informational bias that would be inevitable if only one-time measurements were used. Furthermore, we used the clinical blood glucose level cut points to divide the study cohort into normoglycemic, IGT, and diabetic, enhancing external comparability of our results.

Our study has also weaknesses. The study cohort lacks information on lifestyle factors, such as smoking, diet, and amount of exercise, which may affect PCa progression and cause confounding [24, 25, 26]. However, their role as risk factors for prostate cancer progression is not well established. Additionally, we did not have data on correlates of hyperglycaemia such as hyperinsulinemia or IGF-1 levels, which ultimately could be the drivers of the association found between a high fasting blood glucose levels and the increased risk of PCa death.

In conclusion, diabetic fasting blood glucose levels are associated with poorer PCa outcomes especially among men with localized cancer. Our findings support the role of blood glucose level as risk factor for progression of PCa.

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